DERWENT-ACC-NO: 2001-605294

DERWENT-WEEK: 200169

TITLE: Preparation of high purity **amide-containing guanidine derivatives for e.g. medicines and detergents**

PATENT-ASSIGNEE: LION CORP[LIOY]

PRIORITY-DATA: 1999JP-0377140 (December 28, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2001187775 A	July 10, 2001	N/A	009	C07C 277/08

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
JP2001187775A	N/A	1999JP-0377140	December 28, 1999

INT-CL (IPC): C07C277/08, C07C279/12

ABSTRACTED-PUB-NO: JP2001187775A

BASIC-ABSTRACT:

NOVELTY - Preparation of amide group-having guanidine derivatives or the salts comprises reaction of amideamine or the salts with a guanidine-forming reaction agent, crystallization and filtration and washing with an organic solvent.

DETAILED DESCRIPTION - Preparation of amide group-having guanidine derivatives of formula R1-C(=O)-N(R2)-A-N(R3)-C(=NH)-NH2 (I) or the salts comprises:

(a) reaction of amideamine of formula R1-C(=O)-N(R2)-A-NH(R3) (II) or the salts with a guanidine-forming reaction agent;

(b) crystallization and filtration; and

(c) washing with an organic solvent.

R1 = 1-22C alkyl or alkenyl;

R2, R3 = H, or 1-4C alkyl or hydroxyalkyl;

A = 1-10C alkylene or alkenylene.

USE - Used for cosmetics, medicines for skin use and detergents.

ADVANTAGE - The present high purity amide group-having guanidine derivatives or the salts are stable in aqueous agents containing surface active agents or **electrolytes**.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: PREPARATION HIGH PURE **AMIDE CONTAIN GUANIDINE DERIVATIVE MEDICINE**

DETERGENT

DERWENT-CLASS: B05 D21 D25 E16

CPI-CODES: B10-A17; B10-B02B; B14-N17; B14-R01; D08-B01; D11-D01; E10-A17A;

CHEMICAL-CODES:
Chemical Indexing M2 *01*
Fragmentation Code
C101 C106 C107 C520 C730 C800 C801 C802 C806 C807
M411 M730 M904 M905 M910
Specfic Compounds
01248K 01248S 11339K 11339S
Registry Numbers
1248S 1248U

Chemical Indexing M2 *02*
Fragmentation Code
C017 C100 C800 C801 C803 C804 C805 C806 C807 J0
J011 J3 J371 K0 L2 L250 M225 M231 M262 M281
M312 M321 M332 M342 M383 M391 M411 M510 M520 M530
M540 M620 M640 M720 M904 M905 N272 N332 N361 N512
N513 P943 Q254 Q273
Specfic Compounds
A5HZ6K A5HZ6P

Chemical Indexing M2 *03*
Fragmentation Code
H401 H402 H481 H482 H714 H721 H722 J0 J011 J3
J371 K0 L2 L250 L640 L699 M210 M211 M212 M213
M214 M215 M216 M220 M221 M222 M223 M224 M225 M226
M231 M232 M233 M262 M273 M281 M282 M311 M312 M313
M314 M315 M316 M321 M322 M323 M331 M332 M333 M340
M342 M383 M391 M392 M393 M416 M620 M630 M640 M650
M720 M904 M905 N272 N332 N361 N512 N513 P943 Q254
Q273
Markush Compounds
200049-87601-K 200049-87601-P

UNLINKED-DERWENT-REGISTRY-NUMBERS: 1248S; 1248U

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C2001-179593

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特開2001－187775
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Ｃ０７Ｃ 277/08		Ｃ０７Ｃ 277/08	４Ｈ００６
279/12		279/12	

審査請求　未請求　請求項の数７　書面　（全 9 頁）

(21)出願番号　特願平11－377140

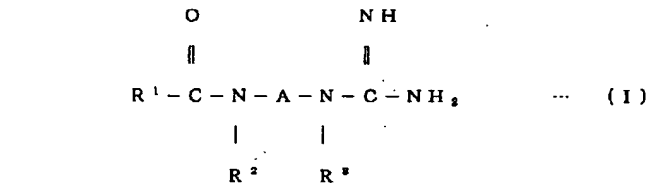
(22)出願日　平成11年12月28日(1999.12.28)

(71)出願人　000006769
ライオン株式会社
東京都墨田区本所１丁目３番７号
(72)発明者　本間　晴城
東京都墨田区本所１丁目３番７号　ライオン株式会社内
(72)発明者　松尾　隆雄
東京都墨田区本所１丁目３番７号　ライオン株式会社内
(72)発明者　植田　茂幸
東京都墨田区本所１丁目３番７号　ライオン株式会社内

最終頁に続く

(54)【発明の名称】　アミド基含有グアニジン誘導体またはその塩の製造方法

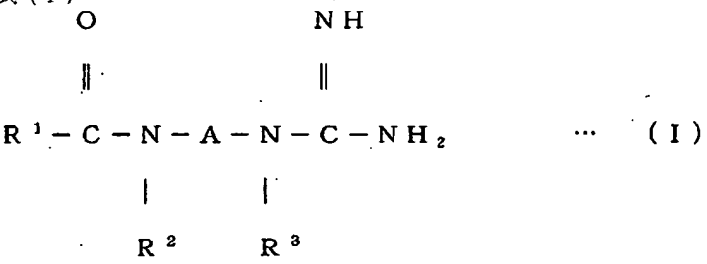
(57)【要約】　（修正有）
【課題】　本発明は、高純度でしかも界面活性剤や電解質共存下においても溶液安定性に優れたアミド基含有グアニジン誘導体またはその塩を安定的に製造する方法を提供することを目的とする。
【解決手段】　下記一般式（Ｉ）
【化１】



で表わされるアミド基含有グアニジン誘導体またはその塩の製造方法であって、アミドアミン及び／またはその塩を、グアニジン化反応試剤を用いてグアニジン化を行う工程、及び、
（２）晶析及び沪過工程、
（３）有機溶媒による洗浄工程を含むことを特徴とするアミド基含有グアニジン誘導体またはその塩の製造方法とする。

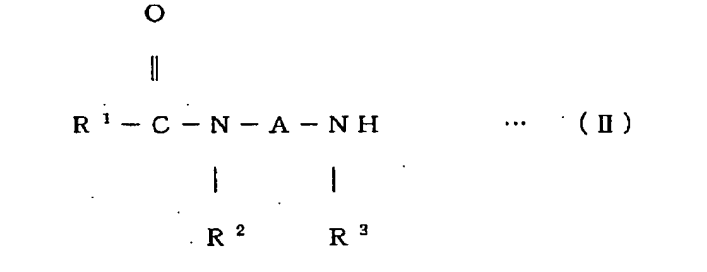
【特許請求の範囲】

【請求項1】下記一般式（Ｉ）



（式中、R^1は、炭素数1～22の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R^2、R^3は、水素原子または炭素数1～4の直鎖または分岐鎖のアルキル基、ヒドロキシルアルキル基であり、同一でも異なっていても良い。Aは、炭素数1～10の直鎖また※は分岐鎖のアルキレン基、あるいはアルケニレン基である。）で表わされるアミド基含有グアニジン誘導体またはその塩の製造方法であって、（1）下記一般式（ＩＩ）

【化2】



（式中、R^1は、炭素数1～22の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R^2、R^3は、水素原子または炭素数1～4の直鎖または分岐鎖のアルキル基、ヒドロキシルアルキル基であり、同一でも異なっていても良い。Aは、炭素数1～10の直鎖または分岐鎖のアルキレン基、あるいはアルケニレン基である。）で表わされるアミドアミン及び／またはその塩を、グアニジン化反応試剤を用いてグアニジン化を行う工程、及び、（2）晶析及び沪過工程、（3）有機溶媒による洗浄工程を含むことを特徴とするアミド基含有グアニジン誘導体またはその塩の製造方法。

【請求項2】グアニジン化反応試剤が、シアナミド、Ｓ－メチルイソチオ尿素、Ｓ－エチルイソチオ尿素、Ｏ－メチルイソチオ尿素、Ｏ－エチルイソチオ尿素から選ばれる1種以上であることを特徴とする請求項1に記載のアミド基含有グアニジン誘導体またはその塩の製造方法。

【請求項3】晶析の溶媒がメチルエチルケトン、テトラヒドロフラン、クロロホルムから選ばれる一種以上であることを特徴とする請求項1又は2に記載のアミド基含有グアニジン誘導体またはその塩の製造方法。

【請求項4】洗浄工程が、メチルエチルケトン、テトラヒドロフラン、クロロホルムから選ばれる一種以上の溶媒による置換洗浄であることを特徴とする請求項1～3に記載のアミド基含有グアニジン誘導体またはその塩の製造方法。

【請求項5】洗浄工程が、メチルエチルケトン、テトラ★ヒドロフラン、クロロホルムから選ばれる1種以上の溶媒による懸濁撹拌洗浄であることを特徴とする請求項1～3に記載のアミド基含有グアニジン誘導体またはその塩の製造方法。

【請求項6】請求項1～5に記載の製造方法で得られたアミド基含有グアニジン誘導体またはその塩を含有する化粧料組成物。

【請求項7】請求項1～5に記載の製造方法で得られたアミド基含有グアニジン誘導体またはその塩を含有する洗浄剤組成物。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、強塩基性を持つグアニジン誘導体を化粧料、洗浄剤等広範囲の用途に適用するための、アミド基を含有するグアニジン誘導体またはその塩の製造方法に関する。

【0002】

【従来の技術】アミド基含有グアニジン誘導体は、皮膚や毛髪等に対する優れたコンディショニング効果を有する基剤であり、例えば特開平6－321727号公報ではこれを含有する保湿性に優れ、かつ使用時の高い延展性（のび）、平滑性を有し、良好な使用感をもつ皮膚外用剤が開示され、特開平6－256146号公報では、アミドアミン界面活性剤との組み合わせにより毛髪になめらかさとしっとり感とを付与する毛髪化粧料が開示されている。また、特開平6－330090ではアニオン基を有する界面活性剤との組み合わせにより、手肌や毛

髪に対するマイルド性、起泡力、すすぎ時のなめらかさ等に優れた洗浄剤組成物が開示されている。しかし、アミド基含有グアニジン誘導体は、合成時に副成するビスアミドやアシル化アミドアミン等の不純物による水性液体製剤への安定性が課題となっていた。これを解決するために、特開平６－３１２９７２号公報では、アミドアミンのグアニジン化反応を行う際に、少量のアルコール類またはエーテル類を存在させて反応を行い、晶析工程で不純物を除去する高純度アミド基含有グアニジン誘導体またはその塩の製造方法が開示されている。この方法により得られた該グアニジン誘導体またはその塩は、約９９．５％程度の高純度な目的生成物が得られ、水および／またはアルコールへの溶解性、安定性に優れている。しかし、なおごく微量残存する不純物の影響と思わ＊れるが、他の活性剤や電解質等を含有する化粧料や洗浄剤等の組成物における安定性は、必ずしも満足できるものではなかった。

【０００３】

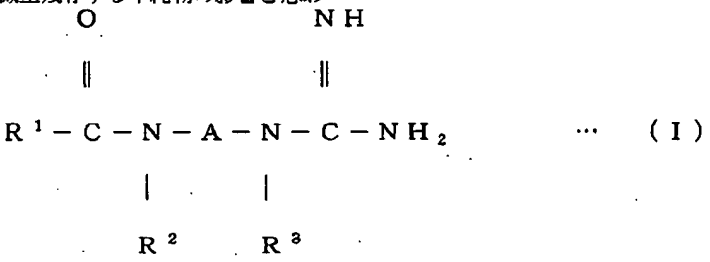
【発明が解決しようとする課題】本発明は、高純度でしかも界面活性剤や電解質共存下においても溶液安定性に優れたアミド基含有グアニジン誘導体またはその塩を安定的に製造する方法を提供することを目的とする。

【０００４】

【課題を解決するための手段】本発明は、高純度の下記一般式（Ｉ）

【０００５】

【化３】

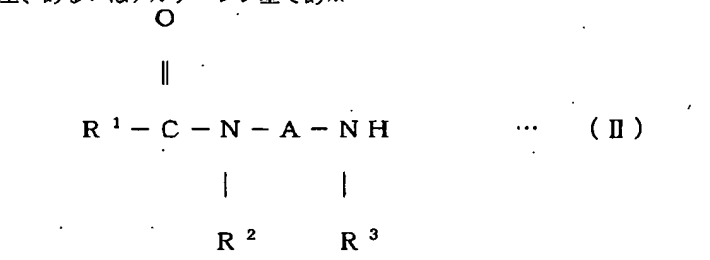


$$R^1-C(=O)-N(R^2)-A-N(R^3)-C(=NH)-NH_2 \quad \cdots \quad (I)$$

（式中、R^1は、炭素数１～２２の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R^2、R^3は、水素原子または炭素数１～４の直鎖または分岐鎖のアルキル基、ヒドロキシルアルキル基であり、同一でも異なっていても良い。Aは、炭素数１～１０の直鎖または分岐鎖のアルキレン基、あるいはアルケニレン基であ※る。）で表わされるアミド基含有グアニジン誘導体またはその塩の製造方法であって、（１）下記一般式（Ｉ）

【０００６】

【化４】



$$R^1-C(=O)-N(R^2)-A-NH \quad \cdots \quad (II)$$

（式中、R^1は、炭素数１～２２の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R^2、R^3は、水素原子または炭素数１～４の直鎖または分岐鎖のアルキル基、ヒドロキシルアルキル基であり、同一でも異なっていても良い。Aは、炭素数１～１０の直鎖または分岐鎖のアルキレン基、あるいはアルケニレン基である。）

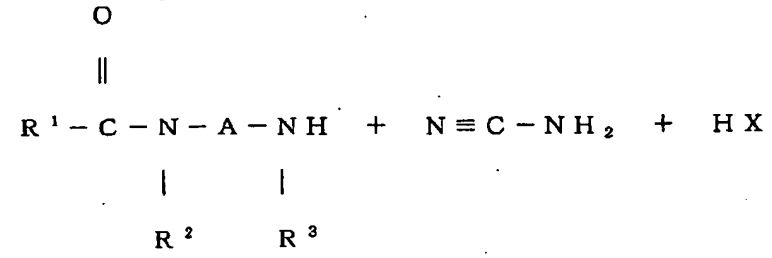
【０００７】で表わされるアミドアミン及び／またはその塩を、グアニジン化反応試剤を用いてグアニジン化を行う工程、及び、（２）晶析及び沪過工程、（３）有機★溶媒による洗浄工程を含むことを特徴とする高純度アミド基含有グアニジン誘導体またはその塩の製造方法が提供される。

【０００８】以下、本発明を詳細に説明する。本発明におけるアミド基含有グアニジン誘導体またはその塩は、以下式１、式２に示す反応式（１）、（２）のような公知の化学反応により合成することができる。

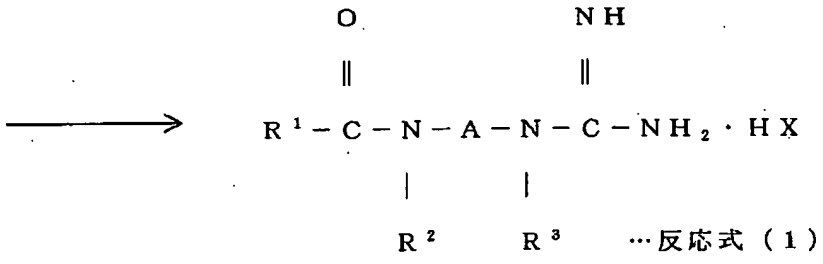
【０００９】

【式１】

5　　6

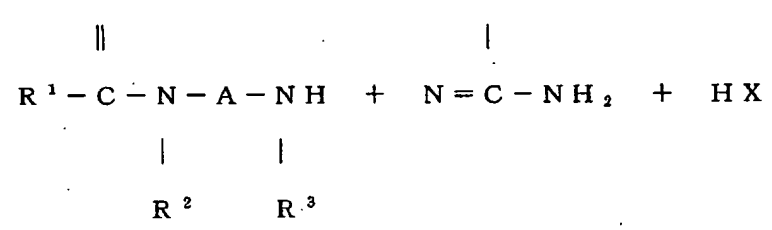


(一般式IIのアミドアミン)　(グアニジン化反応試剤)

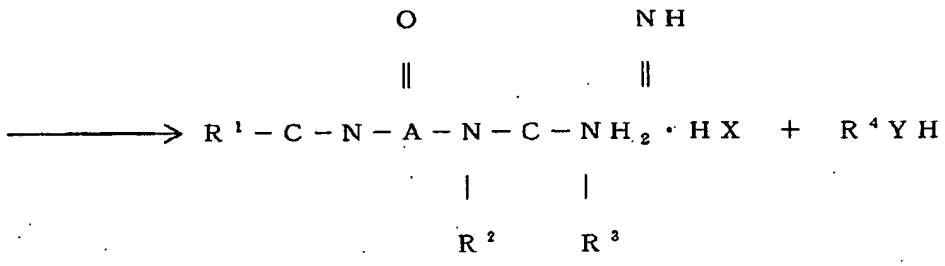


…反応式(1)

【0010】　　*20*【式2】



(一般式IIのアミドアミン)　(グアニジン化反応試剤)



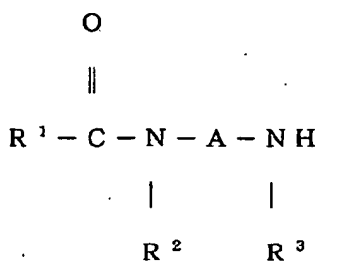
…反応式(2)

(式中、R^1、R^2、R^3およびAは、前記一般式IIと同じ基である。R^4は、炭素数1～4の直鎖または分岐鎖のアルキル基である。HXは、無機酸あるいは有機酸を表わす。Yは、SまたはOである。)

【0011】本発明のアミド基含有グアニジン誘導体ま※たはその塩の製造に用いられるアミドアミンあるいはその塩は、一般式IIで表される化合物、その有機酸あるいは無機酸塩である。

【0012】

【化5】



【0013】式中、R^1は、炭素数1～22、好ましくは8～20、特に好ましくは11～19の直鎖または分岐鎖のアルキル基、あるいはアルケニル基である。R^2、R^3は、水素原子または炭素数1～4の直鎖または分岐鎖のアルキル基、ヒドロキシルアルキル基であり、同一でも異なっていても良い。好ましくは、水素またはメチル基である。Aは、炭素数1～10、好ましくは2～6、特に好ましくは2～4の直鎖または分岐鎖のアルキレン基、あるいはアルケニレン基である。具体的には、例えばモノラウロイルエチレンジアミン、モノラウロイルブチレンジアミン、モノオレオイルエチレンジアミン、モノミリストイルエチレンジアミン、モノステアロイルブチレンジアミン、モノラウロイルヘキシレンジアミン、N-モノラウロイル-N'-メチルエチレンジアミン、N-モノラウロイル-N'-ブチルエチレンジアミン、等があげられる。これらの塩としては、塩酸塩等の無機酸塩、酢酸塩、グリコール酸塩、クエン酸塩、酸性アミノ酸塩等の有機酸塩があげられる。

【0014】本発明で用いられるアミドアミンは、公知の方法で得ることができる。即ち、下記一般式（III）で示される一級および／または二級アミノ基を有するジアミンを、一般式（IV）で示す脂肪酸または脂肪酸エステルによりアシル化した化合物である。

【0015】

【化6】

$R^2-NH-A-NH-R^3$　　…（III）

（式中、R^2、R^3、Aは、一般式（II）で示されるR^2、R^3、Aである。）

【0016】

【化7】

R^1-COOR'　　…（IV）

（式中、R^1は、一般式（II）で示されるR^1である。R'は、水素または炭素数1～3のアルキル基である。）

【0017】ジアミンの具体例としては、ジアミノメタン、エチレンジアミン、N-メチルエチレンジアミン、N，N'-ジメチルエチレンジアミン、N-エチルエチレンジアミン、N，N'-ジエチルエチレンジアミン、N-プロピルエチレンジアミン、N，N'-ジプロピルエチレンジアミン、N-ブチルエチレンジアミン、N，N'-ジブチルエチレンジアミン、N-第三ブチルエチレンジアミン、N，N'-ジ第三ブチルエチレンジアミン、N-メチル-N'-エチルエチレンジアミン、1，2-ジアミノプロパン、1-メチルアミノ-2-アミノプロパン、1-アミノ-2-メチルアミノプロパン、1，3-ジアミノプロパン、1-メチルアミノ-3-アミノプロパン、1，3-ジ（メチルアミノ）プロパン、1-エチルアミノ-3-アミノプロパン、1-プロピルアミノ-3-アミノプロパン、1-ブチルアミノ-3-アミノプロパン、1-第三ブチルアミノ-3-アミノプロパン、1-（2-ヒドロキシエチルアミノ）-3-アミノプロパン、1，2-ジアミノブタン、1，4-ジアミノブタン、1，3-ジアミノ-1-メチルプロパン、1，3-ジアミノ-2-メチルプロパン、1，4-ジアミノ-1-メチルブタン、1，4-ジアミノ-2-メチルブタン、1，6-ジアミノヘキサン、1，8-ジアミノオクタン、1，10-ジアミノデカン等があげられる。これらは単独または2種以上を組合せて使用することができる。

【0018】一般式（IV）で示される脂肪酸または脂肪酸エステルの具体例としては、酢酸、プロピオン酸、酪酸、イソ酪酸、カプロン酸、オクタン酸、カプリン酸、ラウリン酸、ミリスチン酸、パルミチン酸、ステアリン酸、イソステアリン酸、オレイン酸、エライジン酸、リノール酸、リノレン酸、アラキジン酸、ベヘニン酸、やし油脂肪酸、パーム核油脂肪酸、パーム油脂肪酸、牛脂脂肪酸またはそれらのエステル等があげられる。これらは単独または2種以上を組合せて使用することができる。

【0019】アミドアミン塩とする場合は、アミドアミンの対イオンとなる無機酸や有機酸を添加し、好ましくは100℃を超えない温度で、中和すればよい。

【0020】本発明に用いられるグアニジン化反応試剤は、シアナミド、S-メチルイソチオ尿素、S-エチルイソチオ尿素、O-メチルイソ尿素、O-エチルイソ尿素等があげられる。

【0021】本発明の好ましい合成方法としては、窒素等の不活性ガス雰囲気下で、反応温度60～120℃、好ましくは80～100℃で反応を行う。例えば、原料のグアニジン化試剤をイソプロピルアルコール、テトラヒドロフラン等の溶媒に溶解させ、反応系を所定の温度に保ちながら、アミドアミンやその塩に滴下し、滴下終了後、熟成する。その後、必要に応じて中和を行った後、溶媒を留去する。

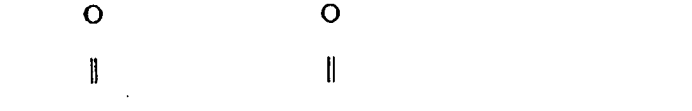
【0022】本発明の目的性生物がアミド基含有グアニジン誘導体塩の場合は、上記のように原料としてアミドアミン塩を用いてグアニジン化しても良いし、アミドアミンをグアニジン化し、その後、酸を用いて中和し塩としても良い。

【0023】本発明方法における高純度アミド基含有グアニジン誘導体またはその塩は、上記の方法等で合成された生成物（粗反応物）を、以下に記載する2段階の方法で精製することにより得られる。

【0024】第一の精製は、晶析＊は、粗反応物に、テトラヒドロフラン、メチルエチルケトン等、目的のグアニジン誘導体の溶解度が温度により大きく変化する溶媒を、粗反応物重量の2～10倍添加し、沸点まで加温する。不溶物が認められれば熱時沪過し、結晶を析出させる所定温度まで徐々に冷却する。結晶析出温度は、主な不純物である下記一般式（V）（VI）の溶解度が0．1質量%となる温度以上に設定することが好ましい。

【0025】

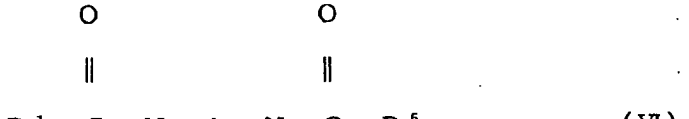
【化8】



（ビスアミド）

【0026】

※20※【化9】



（アシル化アミドアミン）

（VIはグアニジン塩の酸として、有機酸る。）

【0027】十分目的物を析出させた後、温度を維持したまま沪過により溶媒を除去する。沪過は、加圧沪過、フィルタープレス、減圧沪過等、公知の方法で行うことができる。

【0028】本発明における第二の精製は、有機溶媒による洗浄である。有機溶媒は、テトラヒドロフラン、メチルエチルケトン、クロロホルムを好ましく用いることができる。洗浄方法方法としては、押し出し（置換）洗浄あるいは懸濁撹拌洗浄が好ましい。

【0029】押し出し洗浄は、晶析・沪過後、晶析と同じ溶媒を粗反応生成物の2～10倍（重量比）添加して沪過を続けて洗浄をおこなうものである。洗浄溶媒の温度は晶析沪過と同様、一般式（V）（VI）の溶解度が0．1質量%となる温度以上に設定することが好ましい。加える溶媒量は、2倍未満では十分不純物を除去で★きない等の欠点があり、10倍より多い場合は、収率が低く、いずれの場合も好ましくない。懸濁撹拌洗浄は、晶析沪過で得られた湿ケーキを、粗反応生成物重量の2～10倍の晶析と同じ溶媒に添加して、10分～2時間撹拌、分散させた後、再度沪過等により溶媒を除去する。温度は晶析沪過と同様、一般式（V）（VI）の溶解度が0．1質量%となる温度以上に設定することが好ましい。加える溶媒量は、2倍未満では粘度が高くなったり、十分不純物を除去できない等の欠点がある。10倍より多い場合は、収率が低くなる。撹拌洗浄時間は、10分未満では洗浄効果が劣り、また、2時間を越えて撹拌しても洗浄効果は上がらず、経済的に不利である。

【0030】洗浄後の生成物は、真空加熱乾燥など、100℃を超えない温度で定法により乾燥し、本発明の高純度アミド基含有グアニジン誘導体またはその塩を得る。

【0031】以上の2段階精製により得られた高純度アミド基含有グアニジン誘導体またはその塩は、他の界面活性剤や電解質が共存する水性製剤においても安定であり、各種化粧料、皮膚外用剤や洗浄剤に好適に応用することができる。

【0032】

【実施例】（実施例1）　ラウロイルアミドエチルグアニジン塩酸塩の精製

（1）ラウロイルアミドエチルグアニジン塩酸塩の合成

撹拌機、温度計、真空・窒素導入管を備えた500ml四つ口フラスコに、窒素雰囲気下で保存したモノラウロイルエチレンジアミン（アミドアミンと略、純度：97.2%、未反応ラウリン酸：0.8%、ビスアミド：2.0%）121g（0.5モル）を仕込み、80℃に昇温した後、濃塩酸（36%）48.2g（0.475モル）を、系内温度が100℃を越えないように注意しながら滴下、中和した。別に、シアナミド31.5g（0.75モル）をイソプロピルアルコール31.5gに溶解し、アミドアミン95%塩酸塩中に、系内温度を80～90℃に保ちながら1時間かけて滴下した。滴下終了後、同じ温度で3時間熟成を行い、濃塩酸（36%）2.5g（0.025モル）を加え、完全中和した後、溶媒を減圧留去した。収量：170g、液体クロマトグラフおよび薄層クロマトグラフ分析により、アミドアミンからの反応率：93.5%、純度：88.1%、未反応アミドアミン：2.6%、副生ジシアンジアミド：7.0%、ビスアミド：1.4%であった。

【0033】（2）ラウロイルアミドエチルグアニジン塩酸塩の精製

撹拌機、温度計を備えた11四つ口フラスコに。（1）で得た粗生成物100gをとり、テトラヒドロフラン300gを加え、65℃に加熱して粗生成物を完全に溶解した。1℃／分の割合で、25分かけて40℃まで冷却し、結晶が析出してから1時間40℃に保温し、十分結晶を析出させた。加圧沪過器を用いて結晶を沪別した後、40℃のテトラヒドロフラン200gを静かに加え、そのまま沪過、洗浄した。結晶を40℃、2時間真空乾燥して精製ラウロイルアミドエチルグアニジン塩酸塩を得た。収量：74g、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：99.5%、未反応アミドアミン：0.4%、ビスアミド：0.01%、副生ジシアンジアミド：0.1%、であった。この精製品50gをとり、エタノール30g、水20gに溶解したところ、25℃6ヶ月間透明溶液であった。なお、副生したビスアミドの、テトラヒドロフランに対する溶解度は、40℃で0.5%であった。

【0034】（実施例2）　ラウロイルアミドブチルグアニジン酢酸塩の精製

（1）ラウロイルアミドブチルグアニジン酢酸塩の合成

撹拌機、温度計、真空・窒素導入管を備えた500ml四つ口フラスコに、窒素雰囲気下で保存したモノラウロイルブチレンジアミン（アミドアミンと略、純度：98.4%、未反応ラウリン酸：1.0%、ビスアミド：0.6%）135g（0.5モル）を仕込み、80℃に昇温した後、酢酸30g（0.5モル）を、系内温度が100℃を越えないように注意しながら滴下、中和した。別に、シアナミド25.2g（0.6モル）をイソプロピルアルコール25.2gに溶解し、アミドアミン酢酸塩中に、系内温度を80～90℃に保ちながら1時間かけて滴下した。滴下終了後、同じ温度で3時間熟成を行った後、溶媒を減圧留去した。収量：189g、液体クロマトグラフおよび薄層クロマトグラフ分析により、アミドアミンからの反応率：93.8%、純度：92.4%、未反応アミドアミン：1.9%、副生ジシアンジアミド：2.9%、ビスアミド：0.4%、アセチル化アミドアミン：1.6%であった。

【0035】（2）ラウロイルアミドブチルグアニジン酢酸塩の精製

撹拌機、温度計を備えた11四つ口フラスコに。（1）で得た粗生成物100gをとり、メチルエチルケトン500gを加え、80℃に加熱して粗生成物を完全に溶解した。1℃／分の割合で、25分かけて55℃まで冷却し、結晶が析出してから1時間55℃に保温し、十分結晶を析出させた。フィルタープレスを用いて結晶を沪別した後、65℃のメチルエチルケトン500gを通じて沪過、洗浄した。結晶を40℃、2時間真空乾燥して精製ラウロイルアミドブチルグアニジン酢酸塩を得た。収量：61g、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：99.6%、未反応アミドアミン：0.08%、ビスアミド：0.01%以下、副生ジシアンジアミド：0.18%、アセチル化アミドアミン：0.1%、であった。この精製品50gをとり、エタノール30g、水20gに溶解したところ、25℃6ヶ月間透明溶液であった。なお、副生したビスアミドのメチルエチルケトンに対する溶解度は、65℃で0.35%であった。

【0036】（実施例3）　ラウロイルアミドエチルグアニジン酢酸塩の精製

（1）ラウロイルアミドエチルグアニジン酢酸塩の合成

撹拌機、温度計、真空・窒素導入管を備えた500ml四つ口フラスコに、実施例1（1）で用いたと同じモノラウロイルエチレンジアミン121g（0.5モル）を仕込み、80℃に昇温した後、酢酸30g（0.5モル）を、系内温度が100℃を越えないように注意しながら滴下、中和した。別に、シアナミド25.2g（0.6モル）をイソプロピルアルコール25.2gに溶解し、アミドアミン酢酸塩中に、系内温度を80～90℃に保ちながら1時間かけて滴下した。滴下終了後、同じ温度で3時間熟成を行った後、溶媒を減圧留去した。収量：175g、液体クロマトグラフおよび薄層ク

ロマトグラフ分析により、アミドアミンからの反応率：９３．７%、純度：９２．５%、未反応アミドアミン：１．８%、副生ジシアンジアミド：２．８%、ビスアミド：０．８%、アセチル化アミドアミン：１．６%であった。

【００３７】（２）ラウロイルアミドエチルグアニジン酢酸塩の精製

撹拌機、温度計を備えた１１四つ口フラスコに。（１）で得た粗生成物１００ｇをとり、メチルエチルケトン５００ｇを加え、８０℃に加熱して粗生成物を完全に溶解した。1℃／分の割合で、３０分かけて５０℃まで冷却し、結晶が析出してから1時間５０℃に保温し、十分結晶を析出させた。減圧沪過器を用いて結晶を沪別した後、５０℃のメチルエチルケトン３００ｇを静かに加え、そのまま沪過、洗浄した。結晶を４０℃、2時間真空乾燥して精製ラウロイルアミドエチルグアニジン酢酸塩を得た。収量：７０ｇ、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：９９．５%、未反応アミドアミン：０．２%、ビスアミド：０．０１%、副生ジシアンジアミド：０．１６%、アセチル化アミドアミン：０．１%、であった。この精製品５０ｇをとり、エタノール３０ｇ、水２０ｇに溶解したところ、２５℃6ヶ月間透明溶液であった。なお、副生したビスアミドのメチルエチルケトンに対する溶解度は、５０℃で０．２%であった。

【００３８】（実施例４）　ラウロイルアミドブチルグアニジン酢酸塩の精製

撹拌機、温度計を備えた１１四つ口フラスコに。実施例２（１）と同様の方法で得た、ラウロイルアミドブチルグアニジン酢酸塩粗生成物１００ｇをとり、メチルエチルケトン５００ｇを加え、８０℃に加熱して粗生成物を完全に溶解した。1℃／分の割合で、２５分かけて５５℃まで冷却し、結晶が析出してから1時間５５℃に保温し、十分結晶を析出させた。フィルタープレスを用いて結晶を沪別し、１１四つ口フラスコに入れ、メチルエチルケトン５００ｇを加え、６０℃で1時間懸濁撹拌し洗浄した。さらに、フィルタープレスを用いて結晶を沪別し、４０℃、2時間真空乾燥して精製ラウロイルアミドブチルグアニジン酢酸塩を得た。収量：６０ｇ、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：９９．６%、未反応アミドアミン：０．０５%、ビスアミド：０．０１%、副生ジシアンジアミド：０．１６%、アセチル化アミドアミン：０．１%以下、であった。この精製品５０ｇをとり、エタノール３０ｇ、水２０ｇに溶解したところ、２５℃6ヶ月間透明溶液であった。なお、副生したビスアミドのメチルエチルケトンに対する溶解度は、６０℃で０．１６%であった。

*【００３９】（実施例５）　ラウロイルアミドエチルグアニジン塩酸塩の精製

撹拌機、温度計を備えた１１四つ口フラスコに。実施例１（１）と同様の方法で得た、ラウロイルアミドエチルグアニジン塩酸塩粗生成物１００ｇをとり、メチルエチルケトン３００ｇを加え、８０℃に加熱して粗生成物を完全に溶解した。1℃／分の割合で、３０分かけて５０℃まで冷却し、結晶が析出してから1時間５０℃に保温し、十分結晶を析出させた。加圧沪過器を用いて結晶を沪別し、１１四つ口フラスコに入れ、メチルエチルケトン３００ｇを加え、５０℃で1時間懸濁撹拌し洗浄した。さらに、加圧沪過器を用いて結晶を沪別し、４０℃、2時間真空乾燥して精製ラウロイルアミドエチルグアニジン塩酸塩を得た。収量：７４ｇ、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：９９．６%、未反応アミドアミン：０．２%、ビスアミド：０．０１%、副生ジシアンジアミド：０．１２%、であった。この精製品５０ｇをとり、エタノール３０ｇ、水２０ｇに溶解したところ、２５℃6ヶ月間透明溶液であった。なお、副生したビスアミドのメチルエチルケトンに対する溶解度は、５０℃で０．２%であった。

【００４０】（実施例６）　ラウロイルアミドブチルグアニジン酢酸塩の精製

撹拌機、温度計を備えた１１四つ口フラスコに。実施例２（１）と同様の方法で得た、ラウロイルアミドブチルグアニジン酢酸塩粗生成物１００ｇをとり、テトラヒドロフラン５００ｇを加え、６５℃に加熱して粗生成物を完全に溶解した。1℃／分の割合で、４０分かけて２５℃まで冷却し、結晶が析出してから1時間２５℃に保温し、十分結晶を析出させた。遠心沪過器を用いて結晶を沪別し、１１四つ口フラスコに入れ、テトラヒドロフラン３００ｇを加え、２５℃で１．５時間懸濁撹拌し洗浄した。さらに、遠心沪過器を用いて結晶を沪別し、４０℃、2時間真空乾燥して精製ラウロイルアミドブチルグアニジン酢酸塩を得た。収量：８０ｇ、液体クロマトグラフおよび薄層クロマトグラフ分析により、純度：９９．３%、未反応アミドアミン：０．３%、ビスアミド：０．０２%、副生ジシアンジアミド：０．１５%、アセチル化アミドアミン：０．２%、であった。この精製品５０ｇをとり、エタノール３０ｇ、水２０ｇに溶解したところ、２５℃6ヶ月間透明溶液であった。なお、副生したビスアミドのテトラヒドロフランに対する溶解度は、２５℃で０．１%であった。

【００４１】（実施例７）実施例１～６で得たアミド基含有グアニジン塩を用いて、以下のシャンプー組成物を調製した。

本発明品	０．７
ラウリン酸シュガーエステル	１０
Ｎ，Ｎ－ジメチル－Ｎ－ラウリルアミンオキシド	１０

ヤシ油脂肪酸時エタノールアミド	4
安息香酸ナトリウム	0．9
硫酸ナトリウム	2
水	残部

（ｐＨ７：水酸化ナトリウムで調整）

いずれの生成物を用いた場合も、２５℃６ヶ月間、溶液は安定であった。

＊含有グアニジン塩を用いて、以下の台所用洗浄剤組成物を調製した。

【００４２】（実施例８）実施例１～６で得たアミド基＊

本発明品	5
ポリオキシエチレン（ｐ＝３）ラウリル硫酸ナトリウム	25
グリセリン	3
エタノール	7
ヤシ油脂肪酸ジエタノールアミド	5
安息香酸ナトリウム	3
香料	0．4
水	残部

いずれの生成物を用いた場合も、２５℃６ヶ月間、溶液※　※は安定であった。

フロントページの続き

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PATENT ABSTRACTS OF JAPAN

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(71)Applicant : **LION CORP**

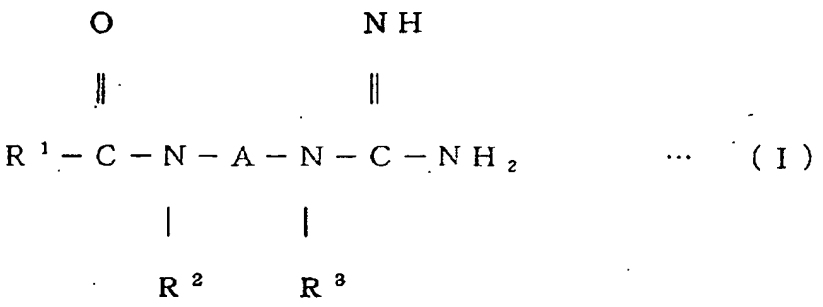
(72)Inventor : **HONMA HARUSHIRO**
MATSUO TAKAO
UEDA SHIGEYUKI

(54) METHOD FOR PRODUCING AMIDE GROUP-CONTAINING GUANIDINE DERIVATIVE OR ITS SALT

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a method for stably producing a high-purity amide group-containing guanidine derivative having excellent solution stability even in the presence of a surfactant and an electrolyte or its salt.
SOLUTION: This method for producing the amide group-containing guanidine derivative of general formula (I) or its salt is characterized in that the method comprises a process for guanidinating an amidoamine and/or its salt with a guanidination reaction reagent, (2) a crystallization and filtration process and (3) a cleaning process with an organic solvent.

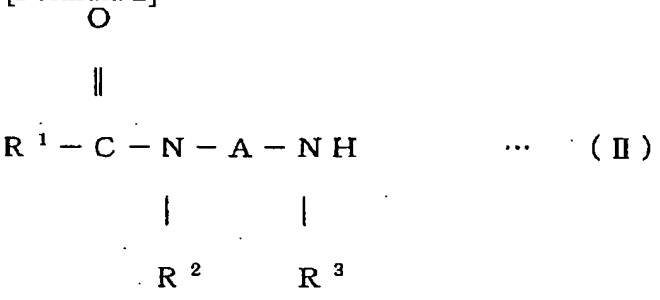
CLAIMS

[Claim(s)]
[Claim 1] The following general formula (I)
[Formula 1]



(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group of the straight chain of carbon numbers 1-10, or branched chain, or an alkenylene group. It is the manufacture approach of the amide group content guanidine derivative expressed or its salt, and is the (1) following general formula (II).

[Formula 2]



(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group of the straight chain of carbon numbers 1-10, or branched chain, or an alkenylene group. The amide group content guanidine derivative characterized by including the process which performs guanidine-ization for the amide amine expressed and/or its salt using a guanidine-ized reaction agent, (2) crystallization and a filtration process, and the washing process by (3) organic solvents, or the manufacture approach of the salt.

[Claim 2] The amide group content guanidine derivative according to claim 1 characterized by a guanidine-ized reaction agent being one or more sorts chosen from a cyanamide, S-methyl iso thiourea, S-ethyl iso thiourea, O-methyl iso thiourea, and O-ethyl iso thiourea, or the manufacture approach of the salt.

[Claim 3] The amide group content guanidine derivative according to claim 1 or 2 characterized by being more than a kind as which the solvent of crystallization is chosen from a methyl ethyl ketone, a tetrahydrofuran, and chloroform, or the manufacture approach of the salt.

[Claim 4] The amide group content guanidine derivative according to claim 1 to 3 characterized by a washing process being the displacement washing by the solvent more than a kind chosen from a methyl ethyl ketone, a tetrahydrofuran, and chloroform, or the manufacture approach of the salt.

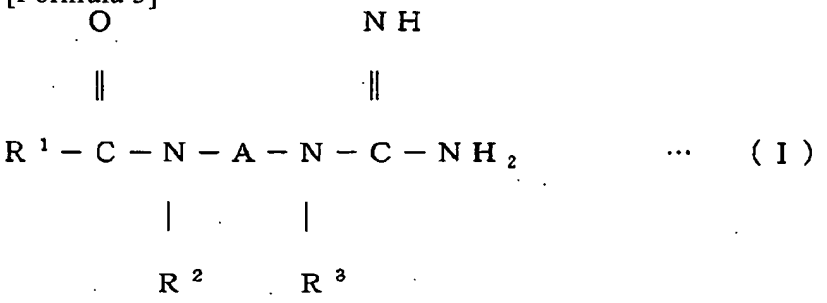
[Claim 5] The amide group content guanidine derivative according to claim 1 to 3 characterized by a washing process being suspension stirring washing by one or more sorts of solvents chosen from a methyl ethyl ketone, a tetrahydrofuran, and chloroform, or the manufacture approach of the salt.

[Claim 6] The cosmetics constituent containing the amide group content guanidine derivative obtained by the manufacture approach according to claim 1 to 5, or its salt.

[Claim 7] The cleaning agent constituent containing the amide group content guanidine derivative obtained by the manufacture approach according to claim 1 to 5, or its salt.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the manufacture approach of the guanidine derivative containing the amide group for applying a guanidine derivative with strong base nature to wide range applications, such as cosmetics and a cleaning agent, or its salt.
[0002]
[Description of the Prior Art] An amide group content guanidine derivative is a basis which has the outstanding conditioning effectiveness over the skin, hair, etc., for example, it excels in the moistness which contains this in JP,6-321727,A, and has the high spread nature at the time of use (mileage), and smooth nature, skin external preparations with a good feeling of use are indicated, and the hair cosmetics which give admiration gently to hair with smoothness with combination with an amide amine surfactant are indicated in JP,6-256146,A. Moreover, in JP,6-330090,A, the cleaning agent constituent which was excellent in the mild nature to a hand skin or hair, the foam formation force, the smoothness at the time of a rinse, etc. with combination with the surfactant which has an anion radical is indicated. However, the stability to the aquosity liquid pharmaceutical preparation by impurities which sub** an amide group content guanidine derivative at the time of composition, such as a bis-amide and an acylation amide amine, had become a technical problem. By JP,6-312972,A, in order to solve this, in case the guanidine-ized reaction of an amide amine is performed, it reacts by making little alcohols or ether exist, and the manufacture approach of the high grade amide group content guanidine derivative from which an impurity is removed with a crystallizing process, or its salt is indicated. About 99.5% of high grade purpose product is obtained, and this guanidine derivative obtained by this approach or its salt is excellent in the solubility to water and/or alcohol, and stability. However, although the effect of an impurity which carries out minute amount survival still very much was seemed, the stability in constituents containing other activators, electrolytes, etc., such as cosmetics and a cleaning agent, was not what can not necessarily be satisfied.
[0003]
[Problem(s) to be Solved by the Invention] This invention aims at offering the approach of manufacturing stably the amide group content guanidine derivative which was moreover excellent in solution stability under a surface active agent or electrolyte coexistence with the high grade, or its salt.
[0004]
[Means for Solving the Problem] This invention is the following general formula (I) of a high grade.
[0005]
[Formula 3]

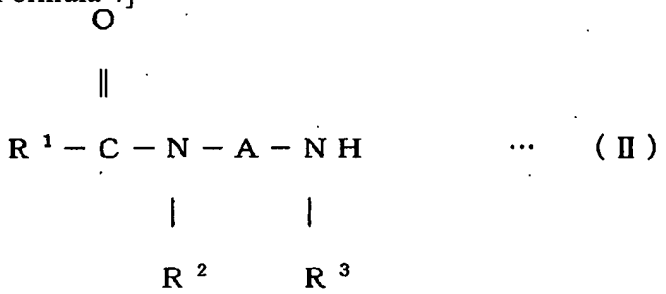


$$R^1-C(=O)-N(R^2)-A-N(R^3)-C(=NH)-NH_2 \quad \cdots \quad (I)$$

(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group of the straight chain of carbon numbers 1-10, or branched chain, or an alkenylene group. It is the manufacture approach of the amide group content guanidine derivative expressed or its salt, and is the (1) following general formula (II).

[0006]

[Formula 4]



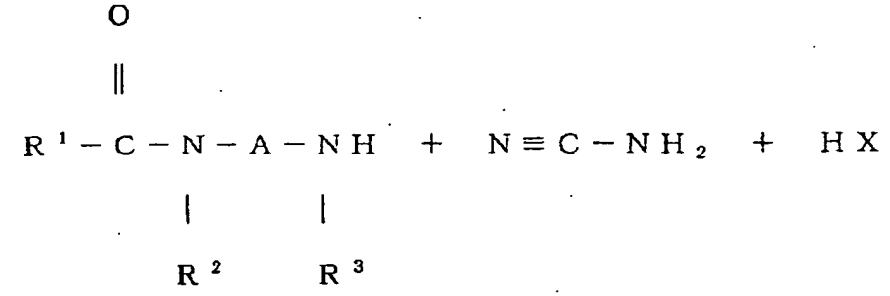
(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group of the straight chain of carbon numbers 1-10, or branched chain, or an alkenylene group.

[0007] The manufacture approach of the high grade amide group content guanidine derivative characterized by including the process which comes out and performs guanidine-ization for the amide amine expressed and/or its salt using a guanidine-ized reaction agent, (2) crystallization and a filtration process, and the washing process by (3) organic solvents, or its salt is offered.

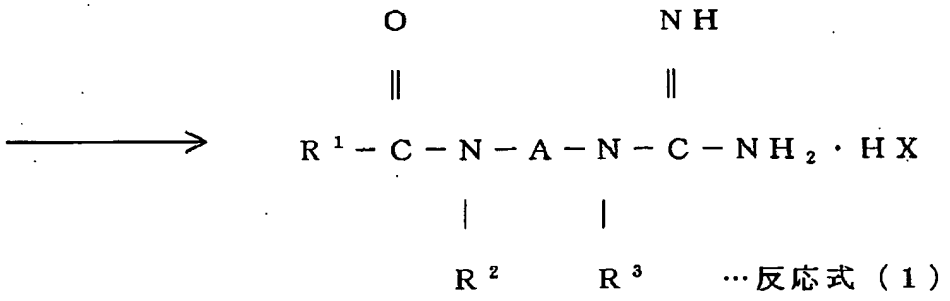
[0008] Hereafter, this invention is explained to a detail. The amide group content guanidine derivative in this invention or its salt is compoundable with the well-known chemical reaction shown in a formula 1 and a formula 2 below as shown in a reaction formula (1) and (2).

[0009]

[Formula 1]

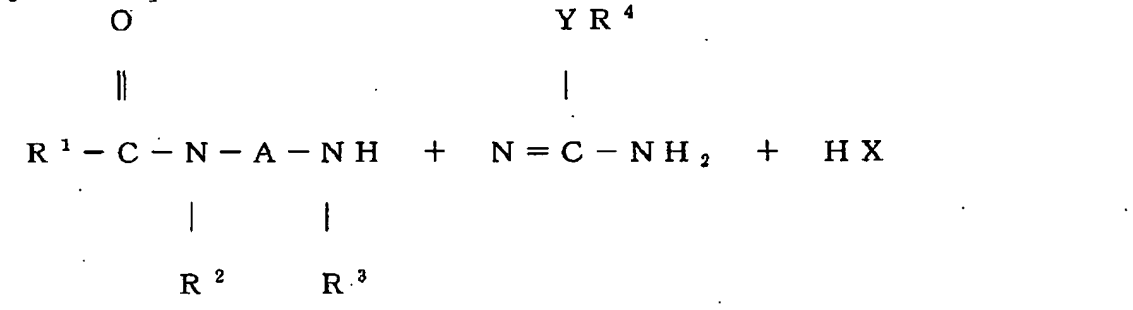


（一般式Ⅱのアミドアミン）（グアニジン化反応試剤）

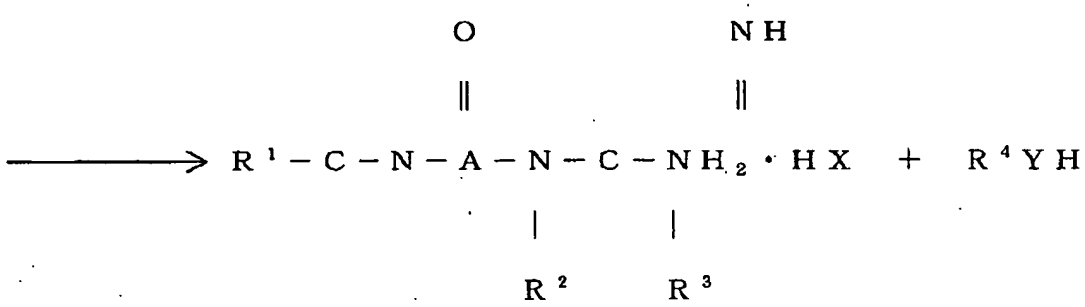


…反応式（１）

[0010]
[Formula 2]



（一般式Ⅱのアミドアミン）（グアニジン化反応試剤）



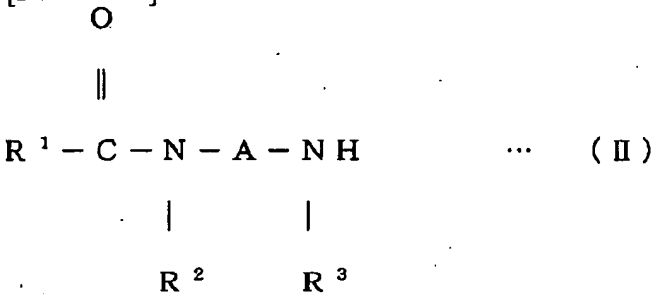
…反応式（２）

(R1, R2, R3, and A are the same radicals as said general formula II among a formula.) R4 is the alkyl group of the straight chain of carbon numbers 1-4, or branched chain. HX expresses an inorganic acid or an organic acid. Y is S or O.

[0011] The amide amine used for manufacture of the amide group content guanidine derivative of this invention or its salt or its salt is the compound expressed with a general formula II, its organic acid, or an inorganic-acid salt.

[0012]

[Formula 5]



[0013] the inside of a formula, and R1 -- carbon numbers 1-22 -- desirable -- 8-20 -- they are the alkyl group of the straight chain of 11-19, or branched chain, or an alkenyl radical especially preferably. R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. Preferably, they are hydrogen or a methyl group. A -- carbon numbers 1-10 -- desirable -- 2-6 -- they are the alkylene group of the straight chain of 2-4, or branched chain, or an alkenylene group especially preferably. concrete -- for example, mono-lauroyl ethylenediamine and mono-lauroyl butylene diamine -- mono--- me -- oil ethylenediamine, mono-myristoyl ethylenediamine, mono-stearoyl butylene diamine, mono-lauroyl hexylene diamine, N-mono-lauroyl-N'- methyl ethylene diamine and N-mono-lauroyl-N'-butyl ethylenediamine, etc. are raised. As these salts, organic-acid salts, such as inorganic-acid salts, such as a hydrochloride, acetate, a glycolic-acid salt, citrate, and an acidic-amino-acid salt, are raised.

[0014] The amide amine used by this invention can be obtained by the well-known approach. That is, it is the compound which acylated the diamine which has the first class and/or the second class amino group which are shown by the following general formula (III) by the fatty acid or fatty acid ester shown by the general formula (IV).

[0015]

[Formula 6]

R2-NH-A-NH-R3 -- (III)

(R2, R3, and A are R2, R3, and A which are shown by the general formula (II) among a formula.)

[0016]

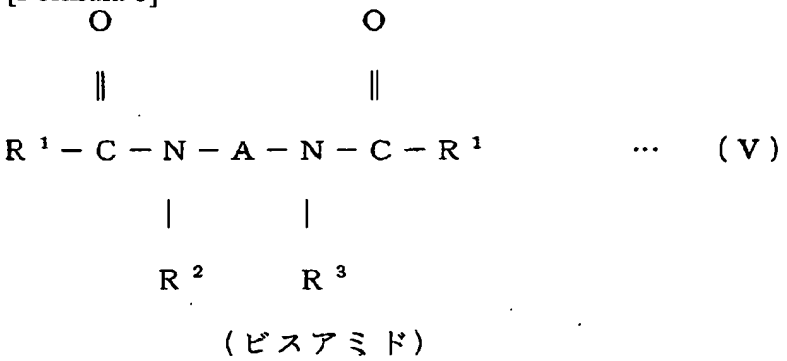
[Formula 7]

R1-COOR' -- (IV)

(R1 is R1 shown by the general formula (II) among a formula.) R' is hydrogen or the alkyl group of carbon numbers 1-3.

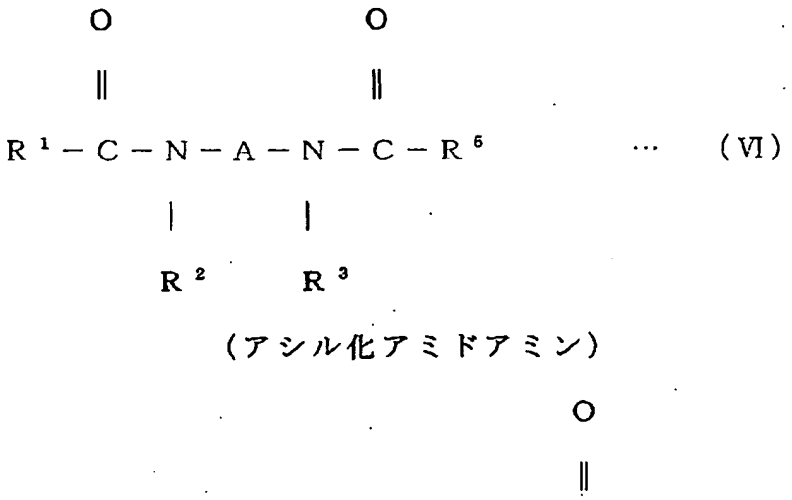
[0017] As an example of diamine, diamino methane, ethylenediamine, N-methyl ethylene diamine, N and N'-dimethyl ethylenediamine, N-ethyl ethylenediamine, N and N'-diethyl ethylenediamine, N-propyl ethylenediamine, N and N'-dipropyl ethylenediamine, N-butyl ethylenediamine, N and N'-dibutyl ethylenediamine, N-tertiary butyl ethylenediamine, N and N'- JI tertiary butyl ethylenediamine and N-methyl-N'-ethyl ethylenediamine, 1, 2-diaminopropane, a 1-methylamino-2-amino propane, A 1-amino-2-methylamino propane, 1, 3-diaminopropane, A 1-methylamino-3-amino propane, 1, 3-JI (methylamino) propane, A 1-ethylamino-3-amino propane, a 1-propylamino-3-amino propane, A 1-butylamino-3-amino propane, a 1-third butylamino-3-amino propane, A 1-(2-hydroxyethylamino)-3-amino propane, 1, 2-diamino butane, A 1,4-diaminobutane, 1, and 3-diamino-1-methyl propane, 1, 3-diamino-isobutane, 1, and 4-diamino-1-methyl butane, 1, 4-diamino-2-methyl butane, 1, 6-diaminohexan, 1, 8-diamino octane, 1, 10-diamino decane, etc. are raised. These can be used

combining independent or two sorts or more.
[0018] As an example of the fatty acid shown by the general formula (IV), or fatty acid ester, an acetic acid, a propionic acid, butanoic acid, an isobutyric acid, a caproic acid, an octanoic acid, a capric acid, a lauric acid, a myristic acid, a palmitic acid, stearin acid, isostearic acid, oleic acid, an elaidic acid, linolic acid, a linolenic acid, arachidic acid, behenic acid, a coconut oil fatty acid, a palm-kernel-oil fatty acid, a palm oil fatty acid, beef tallow fatty acids, or those ester is raised. These can be used combining independent or two sorts or more.
[0019] What is necessary is to add the inorganic acid and organic acid used as the counter ion of an amide amine, to be the temperature which does not exceed 100 degrees C preferably, and just to neutralize, when considering as an amide amine salt.
[0020] As for the guanidine-ized reaction agent used for this invention, a cyanamide, S-methyl iso thiourea, S-ethyl iso thiourea, O-methylisourea, an O-ethyl iso urea, etc. are raised.
[0021] As the desirable synthetic approach of this invention, it reacts at 80-100 degrees C preferably the reaction temperature of 60-120 degrees C under inert gas ambient atmospheres, such as nitrogen. For example, dissolving the guanidine-ized agent of a raw material in solvents, such as isopropyl alcohol and a tetrahydrofuran, and maintaining the system of reaction at predetermined temperature, it is dropped at an amide amine or its salt, and ripes after dropping termination. Then, a solvent is distilled off after neutralizing if needed.
[0022] When the purposiveness living thing of this invention is an amide group content guanidine derivative salt, you may guanidine-ize as mentioned above, using an amide amine salt as a raw material, an amide amine is guanidine-ized, and it neutralizes after that using an acid, and is good also as a salt.
[0023] The high grade amide group content guanidine derivative in this invention approach or its salt is obtained by refining the product (rough reactant) compounded by the above-mentioned approach etc. by two steps of the approaches of indicating below.
[0024] The first purification is crystallization and filtration. Rough reactant weight adds the solvent which changes with temperature a lot two to 10 times to a rough reactant, and the solubility of the guanidine derivative of the purposes, such as a tetrahydrofuran and a methyl ethyl ketone, warms crystallization to it till the boiling point. If insoluble matter is accepted, it will filter at the time of heat, and it cools gradually to the predetermined temperature which deposits a crystal. As for crystal deposit temperature, it is desirable to set up beyond the temperature from which the solubility of the following general formula (V) which are the main impurities, and (VI) becomes 0.1 mass %.
[0025]
[Formula 8]



(ビスアミド)

[0026]
[Formula 9]



(アシル化アミドアミン)

(VIはグアニジン塩の酸として、有機酸　R^5-C-OHを用いた場合に生成す

**.

[0027] After depositing the specified substance enough, filtration removes a solvent, with temperature maintained. Filtration can be performed by well-known approaches, such as pressure filtration, the filter press, and filtration under reduced pressure.

[0028] The second purification in this invention is washing by the organic solvent. A tetrahydrofuran, a methyl ethyl ketone, and chloroform can be preferably used for an organic solvent. As the washing approach approach, it extrudes (permutation) and washing or suspension stirring washing is desirable.

[0029] Knockout washing washes after crystallization and filtration by a rough resultant's carrying out addition of the same solvent as crystallization two to 10 times (weight ratio), and continuing filtration. As for the temperature of a washing solvent, it is desirable to set up like crystallization filtration beyond the temperature from which the solubility of a general formula (V) and (VI) becomes 0.1 mass %. The amount of solvents to apply has a fault with an impurity unremovable enough by under 2 double, when [than 10 times] more, yield is low, and it is not desirable also when it is any. After suspension stirring washing adds to the same solvent as 2 to 10 times as much crystallization as rough resultant weight, and it stirs and it distributes the ** cake obtained by crystallization filtration for 10 minutes to 2 hours, it removes a solvent by filtration etc. again. As for temperature, it is desirable to set up like crystallization filtration beyond the temperature from which the solubility of a general formula (V) and (VI) becomes 0.1 mass %. By under 2 double, viscosity becomes high or the amount of solvents to apply has a fault with an unremovable enough impurity. Yield becomes low when [than 10 times] more. Even if churning washing time amount is inferior in a cleaning effect in less than 10 minutes and it agitates exceeding 2 hours, a cleaning effect does not go up but is economically disadvantageous.

[0030] the temperature to which the product after washing does not exceed 100 degrees C, such as vacuum stoving, -- a law -- it dries by the method and the high grade amide group content guanidine derivative of this invention or its salt is obtained.

[0031] The high grade amide group content guanidine derivative obtained by the above two-step purification or its salt is stable also in the aquosity pharmaceutical preparation with which other surfactants and electrolytes live together, and can be applied suitable for various cosmetics, skin external preparations, or a cleaning agent.

[0032]

[Example] (Example 1) The synthetic agitator of the purification (1) lauroyl amide ethyl guanidine hydrochloride of a lauroyl amide ethyl guanidine hydrochloride, Mono-lauroyl ethylenediamine saved under nitrogen-gas-atmosphere mind in 500ml 4 opening flask equipped with a thermometer, and a

vacuum and nitrogen installation tubing (an amide amine and abbreviation) purity: -- unreacted 97.2% -- lauric-acid:0.8% -- bis--- after teaching amide:2.0%121g (0.5 mols) and carrying out a temperature up to 80 degrees C, it dropped and neutralized, being careful of 48.2g (36%) (0.475 mols) of concentrated hydrochloric acid for whenever [system internal temperature] not to exceed 100 degrees C. another -- cyanamide 31.5g (0.75 mols) -- isopropyl alcohol 31.5g -- dissolving -- amide amine 95% -- it was dropped over 1 hour into the hydrochloride, keeping whenever [system internal temperature] at 80-90 degrees C. Aging was performed at the same temperature after dropping termination for 3 hours, and after adding and carrying out full neutralization of the 2.5g (36%) (0.025 mols) of the concentrated hydrochloric acid, reduced pressure distilling off of the solvent was carried out. yield: -- 170g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.5% from an amide amine, and purity: -- unreacted 88.1% -- amide amine:2.6% and byproduction dicyandiamide:7.0% -- bis--- it was amide:1.4%.

[0033] (2) In the purification agitator of a lauroyl amide ethyl guanidine hydrochloride, and 11 4 opening flask equipped with the thermometer 100g of rough products obtained by (1) was taken, tetrahydrofuran 300g was added, it heated at 65 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 40 degrees C over 25 minutes, after the crystal deposited, it was kept warm at 40 degrees C for 1 hour, and the crystal was deposited enough. After carrying out a crystal a ** exception using a pressure filter, it added calmly, and as it was, it filtered and 40-degree C tetrahydrofuran 200g was washed. The vacuum drying of the 40 degrees C of the crystals was carried out for 2 hours, and the purification lauroyl amide ethyl guanidine hydrochloride was obtained. yield: -- 74g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.5% -- amide amine:0.4% -- bis--- amide:0.01% and byproduction dicyandiamide: -- it came out 0.1%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the tetrahydrofuran of the bis-amide which carried out the byproduction was 0.5% at 40 degrees C.

[0034] (Example 2) The synthetic agitator of the purification (1) lauroyl amide butyl guanidine-acetic acid salt of a lauroyl amide butyl guanidine-acetic acid salt, Mono-lauroyl butylene diamine saved under nitrogen-gas-atmosphere mind in 500ml 4 opening flask equipped with a thermometer, and a vacuum and nitrogen installation tubing (an amide amine and abbreviation) purity: -- unreacted 98.4% -- lauric-acid:1.0% -- bis--- after teaching amide:0.6%135g (0.5 mols) and carrying out a temperature up to 80 degrees C, it dropped and neutralized, being careful of 30g (0.5 mols) of acetic acids for whenever [system internal temperature] not to exceed 100 degrees C. Independently, cyanamide 25.2g (0.6 mols) was dissolved in isopropyl alcohol 25.2g, and it was dropped over 1 hour into amide amine acetate, keeping whenever [system internal temperature] at 80-90 degrees C. After dropping termination, after performing aging at the same temperature for 3 hours, reduced pressure distilling off of the solvent was carried out. yield: -- 189g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.8% from an amide amine, and purity: -- unreacted 92.4% -- amide amine:1.9% and byproduction dicyandiamide:2.9% -- bis--- they were amide:0.4% and acetylation amide amine:1.6%.

[0035] (2) In the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and 11 4 opening flask equipped with the thermometer 100g of rough products obtained by (1) was taken, methyl-ethyl-ketone 500g was added, it heated at 80 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 55 degrees C over 25 minutes, after the crystal deposited, it was kept warm at 55 degrees C for 1 hour, and the crystal was deposited enough. After carrying out a crystal a ** exception using a filter press, 65-degree C methyl-ethyl-ketone 500g was led and washed [filtered and]. The vacuum drying of the 40 degrees C of the crystals was carried out for 2 hours, and the purification lauroyl amide butyl guanidine-acetic acid salt was obtained. yield: -- 61g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.6% -- amide amine:0.08% -- bis--- less than [amide:0.01%], byproduction dicyandiamide:0.18%, and

acetylation amide amine: -- it came out 0.1%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.35% at 65 degrees C.

[0036] (Example 3) The synthetic agitator of the purification (1) lauroyl amide ethyl guanidine-acetic acid salt of a lauroyl amide ethyl guanidine-acetic acid salt, The same mono-lauroyl ethylenediamine 121g (0.5 mols) is taught with having used for 500ml 4 opening flask equipped with a thermometer, and a vacuum and nitrogen installation tubing in the example 1 (1). After carrying out a temperature up to 80 degrees C, it dropped and neutralized, being careful of 30g (0.5 mols) of acetic acids for whenever [system internal temperature] not to exceed 100 degrees C. Independently, cyanamide 25.2g (0.6 mols) was dissolved in isopropyl alcohol 25.2g, and it was dropped over 1 hour into amide amine acetate, keeping whenever [system internal temperature] at 80-90 degrees C. After dropping termination, after performing aging at the same temperature for 3 hours, reduced pressure distilling off of the solvent was carried out. yield: -- 175g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.7% from an amide amine, and purity: -- unreacted 92.5% -- amide amine:1.8% and byproduction dicyandiamide:2.8% -- bis--- they were amide:0.8% and acetylation amide amine:1.6%.

[0037] (2) In the purification agitator of a lauroyl amide ethyl guanidine-acetic acid salt, and 11 4 opening flask equipped with the thermometer 100g of rough products obtained by (1) was taken, methyl-ethyl-ketone 500g was added, it heated at 80 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 50 degrees C over 30 minutes, after the crystal deposited, it was kept warm at 50 degrees C for 1 hour, and the crystal was deposited enough. After carrying out a crystal a ** exception using a vacuum filter, it added calmly, and as it was, it filtered and 50-degree C methyl-ethyl-ketone 300g was washed. The vacuum drying of the 40 degrees C of the crystals was carried out for 2 hours, and the purification lauroyl amide ethyl guanidine-acetic acid salt was obtained. yield: -- 70g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.5% -- amide amine:0.2% -- bis--- amide:0.01%, byproduction dicyandiamide:0.16%, and acetylation amide amine: -- it came out 0.1%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.2% at 50 degrees C.

[0038] (Example 4) In the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and 11 4 opening flask equipped with the thermometer 100g of lauroyl amide butyl guanidine acetate [which was obtained by the same approach as an example 2 (1)] rough products was taken, methyl-ethyl-ketone 500g was added, it heated at 80 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 55 degrees C over 25 minutes, after the crystal deposited, it was kept warm at 55 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception using the filter press, it put into 11 4 opening flask, and methyl-ethyl-ketone 500g was added, and at 60 degrees C, suspension churning was carried out for 1 hour, and it washed. Furthermore, the crystal was carried out the ** exception using the filter press, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide butyl guanidine-acetic acid salts were obtained. yield: -- 60g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.6% -- amide amine:0.05% -- bis--- amide:0.01%, byproduction dicyandiamide:0.16%, and acetylation amide amine: -- it came out 0.1% or less. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.16% at 60 degrees C.

[0039] (Example 5) In the purification agitator of a lauroyl amide ethyl guanidine hydrochloride, and 11 4 opening flask equipped with the thermometer 100g of lauroyl amide ethyl guanidine

hydrochloride [which was obtained by the same approach as an example 1 (1)] rough products was taken, methyl-ethyl-ketone 300g was added, it heated at 80 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 50 degrees C over 30 minutes, after the crystal deposited, it was kept warm at 50 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception using the pressure filter, it put into 11 4 opening flask, and methyl-ethyl-ketone 300g was added, and at 50 degrees C, suspension churning was carried out for 1 hour, and it washed. Furthermore, the crystal was carried out the ** exception using the pressure filter, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide ethyl guanidine hydrochlorides were obtained. yield: -- 74g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.6% -- amide amine:0.2% -- bis--- amide:0.01% and byproduction dicyandiamide: -- it came out 0.12%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.2% at 50 degrees C.

[0040] (Example 6) In the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and 11 4 opening flask equipped with the thermometer 100g of lauroyl amide butyl guanidine acetate [which was obtained by the same approach as an example 2 (1)] rough products was taken, tetrahydrofuran 500g was added, it heated at 65 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 25 degrees C over 40 minutes, after the crystal deposited, it was kept warm at 25 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception using the centrifugal filtration machine, it put into 11 4 opening flask, and tetrahydrofuran 300g was added, and at 25 degrees C, suspension churning was carried out for 1.5 hours, and it washed. Furthermore, the crystal was carried out the ** exception using the centrifugal filtration machine, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide butyl guanidine-acetic acid salts were obtained. yield: -- 80g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.3% -- amide amine:0.3% -- bis--- amide:0.02%, byproduction dicyandiamide:0.15%, and acetylation amide amine: -- it came out 0.2%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the tetrahydrofuran of the bis-amide which carried out the byproduction was 0.1% at 25 degrees C.

[0041] (Example 7) The following shampoo constituents were prepared using the amide group content guanidine salt obtained in the examples 1-6.

this invention article 0.7 Lauric-acid sugar ester 10 N and N-dimethyl-N-lauryl amine oxide 10 At the time of palm oil fatty acid, ethanol amide 4 Sodium benzoate 0.9 Sodium sulfate 2 Water Remainder (pH7: adjust by the sodium hydroxide)

Also when which product was used, 25-degree-C six-month Hazama and a solution were stable.

[0042] (Example 8) The following cleaning agent constituents for kitchens were prepared using the amide group content guanidine salt obtained in the examples 1-6.

this invention article 5 Polyoxyethylene (p= 3) sodium lauryl sulfate 25 Glycerol 3 Ethanol 7 Palm-oil-fatty-acid diethanolamide 5 Sodium benzoate 3 Perfume 0.4 Water the remainder -- also when which product was used, 25-degree-C six-month Hazama and a solution were stable.

TECHNICAL FIELD

[Industrial Application] This invention relates to the manufacture approach of the guanidine derivative containing the amide group for applying a guanidine derivative with strong base nature to wide range applications, such as cosmetics and a cleaning agent, or its salt.

PRIOR ART

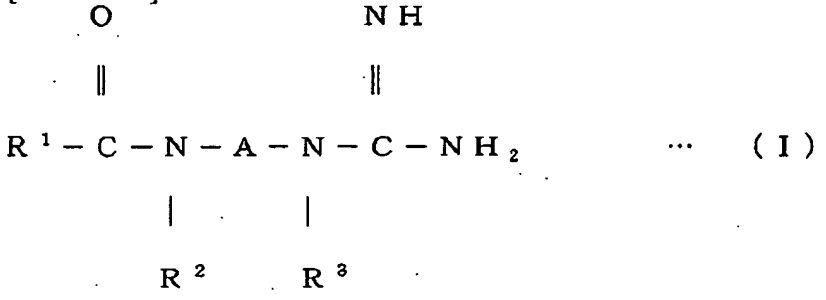
[Description of the Prior Art] An amide group content guanidine derivative is a basis which has the outstanding conditioning effectiveness over the skin, hair, etc., for example, it excels in the moistness which contains this in JP,6-321727,A, and has the high spread nature at the time of use (mileage), and smooth nature, skin external preparations with a good feeling of use are indicated, and the hair cosmetics which give admiration gently to hair with smoothness with combination with an amide amine surfactant are indicated in JP,6-256146,A. Moreover, in JP,6-330090,A, the cleaning agent constituent which was excellent in the mild nature to a hand skin or hair, the foam formation force, the smoothness at the time of a rinse, etc. with combination with the surfactant which has an anion radical is indicated. However, the stability to the aquosity liquid pharmaceutical preparation by impurities which sub** an amide group content guanidine derivative at the time of composition, such as a bis-amide and an acylation amide amine, had become a technical problem. By JP,6-312972,A, in order to solve this, in case the guanidine-ized reaction of an amide amine is performed, it reacts by making little alcohols or ether exist, and the manufacture approach of the high grade amide group content guanidine derivative from which an impurity is removed with a crystallizing process, or its salt is indicated. About 99.5% of high grade purpose product is obtained, and this guanidine derivative obtained by this approach or its salt is excellent in the solubility to water and/or alcohol, and stability. However, although the effect of an impurity which carries out minute amount survival still very much was seemed, the stability in constituents containing other activators, electrolytes, etc., such as cosmetics and a cleaning agent, was not what can not necessarily be satisfied.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] This invention aims at offering the approach of manufacturing stably the amide group content guanidine derivative which was moreover excellent in solution stability under a surface active agent or electrolyte coexistence with the high grade, or its salt.

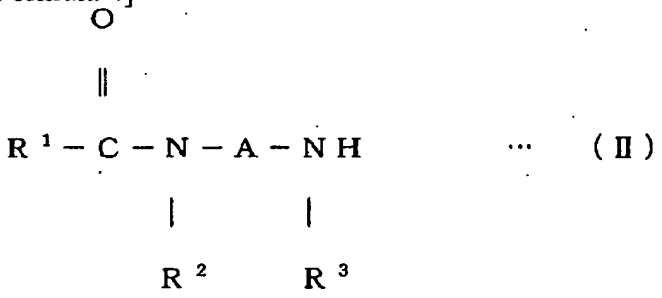
MEANS

[Means for Solving the Problem] This invention is the following general formula (I) of a high grade.
[0005]
[Formula 3]

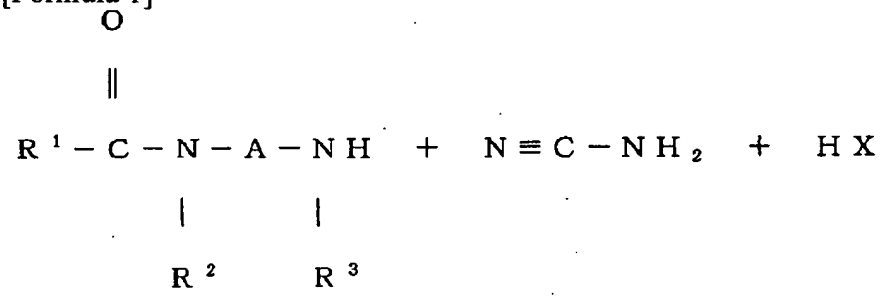


(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group of the straight chain of carbon numbers 1-10, or branched chain, or an

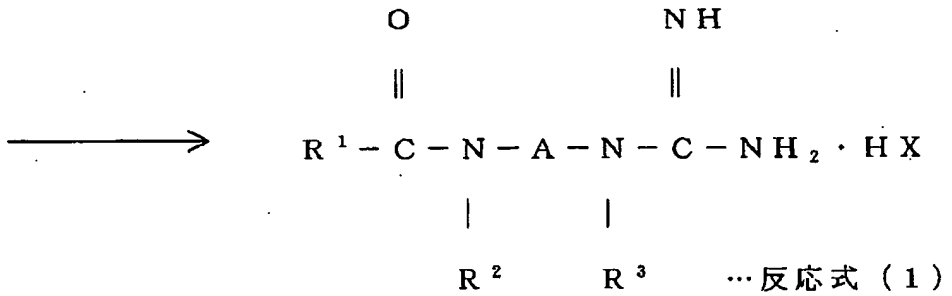
alkenylene group. It is the manufacture approach of the amide group content guanidine derivative expressed or its salt, and is the (1) following general formula (II).
[0006]
[Formula 4]



(R1 is the alkyl group of the straight chain of carbon numbers 1-22, or branched chain, or an alkenyl radical among a formula.) R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. A is the alkylene group of the straight chain of carbon numbers 1-10, or branched chain, or an alkenylene group.
[0007] The manufacture approach of the high grade amide group content guanidine derivative characterized by including the process which comes out and performs guanidine-ization for the amide amine expressed and/or its salt using a guanidine-ized reaction agent, (2) crystallization and a filtration process, and the washing process by (3) organic solvents, or its salt is offered.
[0008] Hereafter, this invention is explained to a detail. The amide group content guanidine derivative in this invention or its salt is compoundable with the well-known chemical reaction shown in a formula 1 and a formula 2 below as shown in a reaction formula (1) and (2).
[0009]
[Formula 1]

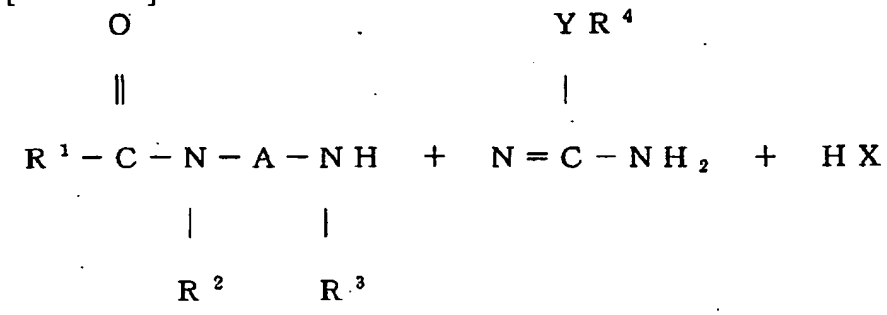


(一般式IIのアミドアミン) (グアニジン化反応試剤)

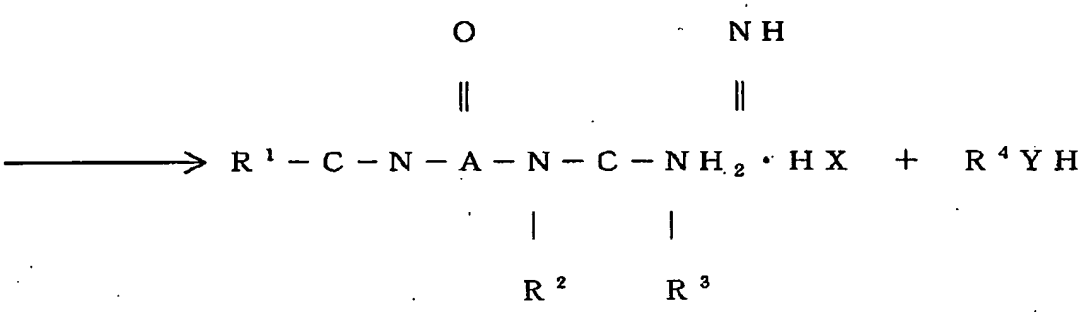


[0010]

[Formula 2]



（一般式Ⅱのアミドアミン）（グアニジン化反応試剤）



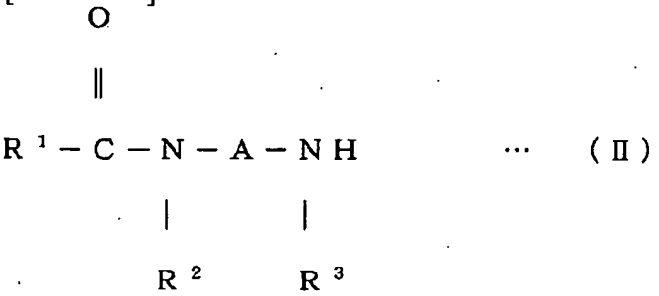
…反応式（２）

(R1, R2, R3, and A are the same radicals as said general formula II among a formula.) R4 is the alkyl group of the straight chain of carbon numbers 1-4, or branched chain. HX expresses an inorganic acid or an organic acid. Y is S or O.

[0011] The amide amine used for manufacture of the amide group content guanidine derivative of this invention or its salt or its salt is the compound expressed with a general formula II, its organic acid, or an inorganic-acid salt.

[0012]

[Formula 5]



[0013] the inside of a formula, and R1 -- carbon numbers 1-22 -- desirable -- 8-20 -- they are the alkyl group of the straight chain of 11-19, or branched chain, or an alkenyl radical especially preferably. R2 and R3 are the alkyl group of the straight chain of a hydrogen atom or carbon numbers 1-4, or branched chain, and a hydroxyl alkyl group, and even if the same, they may differ. Preferably, they are hydrogen or a methyl group. A -- carbon numbers 1-10 -- desirable -- 2-6 -- they are the alkylene group of the straight chain of 2-4, or branched chain, or an alkenylene group especially preferably. concrete -- for example, mono-lauroyl ethylenediamine and mono-lauroyl butylene diamine -- mono--- me -- oil ethylenediamine, mono-myristoyl ethylenediamine, mono-stearoyl butylene diamine, mono-lauroyl

hexylene diamine, N-mono-lauroyl-N'- methyl ethylene diamine and N-mono-lauroyl-N'-butyl ethylenediamine, etc. are raised. As these salts, organic-acid salts, such as inorganic-acid salts, such as a hydrochloride, acetate, a glycolic-acid salt, citrate, and an acidic-amino-acid salt, are raised.

[0014] The amide amine used by this invention can be obtained by the well-known approach. That is, it is the compound which acylated the diamine which has the first class and/or the second class amino group which are shown by the following general formula (III) by the fatty acid or fatty acid ester shown by the general formula (IV).

[0015]

[Formula 6]

R2-NH-A-NH-R3 -- (III)

(R2, R3, and A are R2, R3, and A which are shown by the general formula (II) among a formula.)

[0016]

[Formula 7]

R1-COOR' -- (IV)

(R1 is R1 shown by the general formula (II) among a formula.) R' is hydrogen or the alkyl group of carbon numbers 1-3.

[0017] As an example of diamine, diamino methane, ethylenediamine, N-methyl ethylene diamine, N and N'-dimethyl ethylenediamine, N-ethyl ethylenediamine, N and N'-diethyl ethylenediamine, N-propyl ethylenediamine, N and N'-dipropyl ethylenediamine, N-butyl ethylenediamine, N and N'-dibutyl ethylenediamine, N-tertiary butyl ethylenediamine, N and N'- JI tertiary butyl ethylenediamine and N-methyl-N'-ethyl ethylenediamine, 1, 2-diaminopropane, a 1-methylamino-2-amino propane, A 1-amino-2-methylamino propane, 1, 3-diaminopropane, A 1-methylamino-3-amino propane, 1, 3-JI (methylamino) propane, A 1-ethylamino-3-amino propane, a 1-propylamino-3-amino propane, A 1-butylamino-3-amino propane, a 1-third butylamino-3-amino propane, A 1-(2-hydroxyethylamino)-3-amino propane, 1, 2-diamino butane, A 1,4-diaminobutane, 1, and 3-diamino-1-methyl propane, 1, 3-diamino-isobutane, 1, and 4-diamino-1-methyl butane, 1, 4-diamino-2-methyl butane, 1, 6-diaminohexan, 1, 8-diamino octane, 1, 10-diamino decane, etc. are raised. These can be used combining independent or two sorts or more.

[0018] As an example of the fatty acid shown by the general formula (IV), or fatty acid ester, an acetic acid, a propionic acid, butanoic acid, an isobutyric acid, a caproic acid, an octanoic acid, a capric acid, a lauric acid, a myristic acid, a palmitic acid, stearin acid, isostearic acid, oleic acid, an elaidic acid, linolic acid, a linolenic acid, arachidic acid, behenic acid, a coconut oil fatty acid, a palm-kernel-oil fatty acid, a palm oil fatty acid, beef tallow fatty acids, or those ester is raised. These can be used combining independent or two sorts or more.

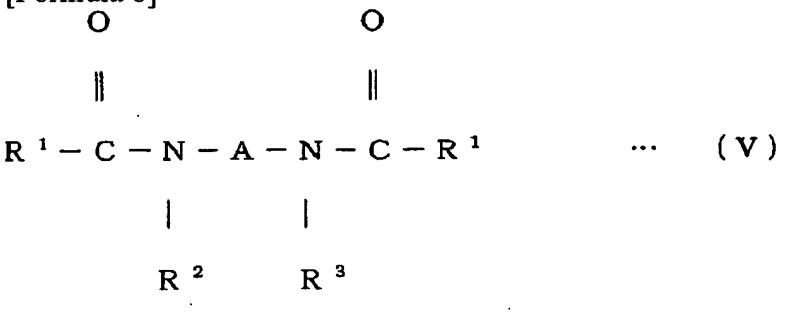
[0019] What is necessary is to add the inorganic acid and organic acid used as the counter ion of an amide amine, to be the temperature which does not exceed 100 degrees C preferably, and just to neutralize, when considering as an amide amine salt.

[0020] As for the guanidine-ized reaction agent used for this invention, a cyanamide, S-methyl iso thiourea, S-ethyl iso thiourea, O-methylisourea, an O-ethyl iso urea, etc. are raised.

[0021] As the desirable synthetic approach of this invention, it reacts at 80-100 degrees C preferably the reaction temperature of 60-120 degrees C under inert gas ambient atmospheres, such as nitrogen. For example, dissolving the guanidine-ized agent of a raw material in solvents, such as isopropyl alcohol and a tetrahydrofuran, and maintaining the system of reaction at predetermined temperature, it is dropped at an amide amine or its salt, and ripes after dropping termination. Then, a solvent is distilled off after neutralizing if needed.

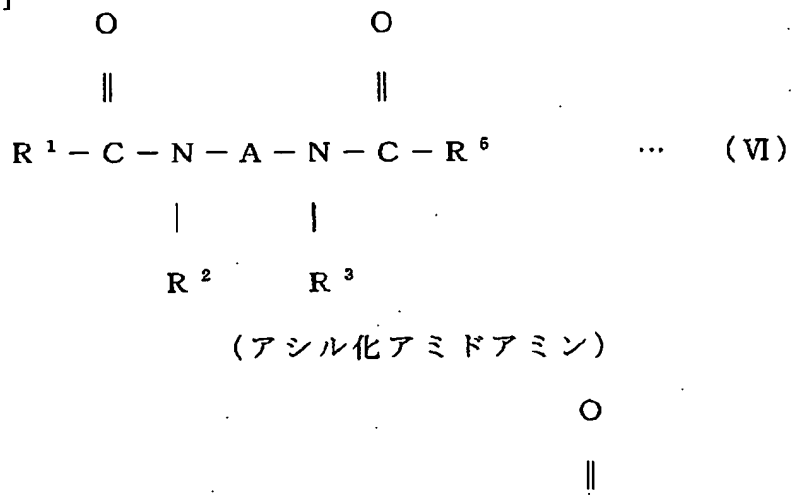
[0022] When the purposiveness living thing of this invention is an amide group content guanidine derivative salt, you may guanidine-ize as mentioned above, using an amide amine salt as a raw material, an amide amine is guanidine-ized, and it neutralizes after that using an acid, and is good also as a salt.

[0023] The high grade amide group content guanidine derivative in this invention approach or its salt is obtained by refining the product (rough reactant) compounded by the above-mentioned approach etc. by two steps of the approaches of indicating below.
[0024] The first purification is crystallization and filtration. Rough reactant weight adds the solvent which changes with temperature a lot two to 10 times to a rough reactant, and the solubility of the guanidine derivative of the purposes, such as a tetrahydrofuran and a methyl ethyl ketone, warms crystallization to it till the boiling point. If insoluble matter is accepted, it will filter at the time of heat, and it cools gradually to the predetermined temperature which deposits a crystal. As for crystal deposit temperature, it is desirable to set up beyond the temperature from which the solubility of the following general formula (V) which are the main impurities, and (VI) becomes 0.1 mass %.
[0025]
[Formula 8]



(ビスアミド)

[0026]
[Formula 9]



(VIはグアニジン塩の酸として、有機酸　R^5-C-OHを用いた場合に生成す

**.
[0027] After depositing the specified substance enough, filtration removes a solvent, with temperature maintained. Filtration can be performed by well-known approaches, such as pressure filtration, the filter press, and filtration under reduced pressure.
[0028] The second purification in this invention is washing by the organic solvent. A tetrahydrofuran, a methyl ethyl ketone, and chloroform can be preferably used for an organic solvent. As the washing approach approach, it extrudes (permutation) and washing or suspension stirring washing is desirable.
[0029] Knockout washing washes after crystallization and filtration by a rough resultant's carrying out

addition of the same solvent as crystallization two to 10 times (weight ratio), and continuing filtration. As for the temperature of a washing solvent, it is desirable to set up like crystallization filtration beyond the temperature from which the solubility of a general formula (V) and (VI) becomes 0.1 mass %. The amount of solvents to apply has a fault with an impurity unremovable enough by under 2 double, when [than 10 times] more, yield is low, and it is not desirable also when it is any. After suspension stirring washing adds to the same solvent as 2 to 10 times as much crystallization as rough resultant weight, and it stirs and it distributes the ** cake obtained by crystallization filtration for 10 minutes to 2 hours, it removes a solvent by filtration etc. again. As for temperature, it is desirable to set up like crystallization filtration beyond the temperature from which the solubility of a general formula (V) and (VI) becomes 0.1 mass %. By under 2 double, viscosity becomes high or the amount of solvents to apply has a fault with an unremovable enough impurity. Yield becomes low when [than 10 times] more. Even if churning washing time amount is inferior in a cleaning effect in less than 10 minutes and it agitates exceeding 2 hours, a cleaning effect does not go up but is economically disadvantageous.

[0030] the temperature to which the product after washing does not exceed 100 degrees C, such as vacuum stoving, -- a law -- it dries by the method and the high grade amide group content guanidine derivative of this invention or its salt is obtained.

[0031] The high grade amide group content guanidine derivative obtained by the above two-step purification or its salt is stable also in the aquosity pharmaceutical preparation with which other surfactants and electrolytes live together, and can be applied suitable for various cosmetics, skin external preparations, or a cleaning agent.

EXAMPLE

[Example] (Example 1) The synthetic agitator of the purification (1) lauroyl amide ethyl guanidine hydrochloride of a lauroyl amide ethyl guanidine hydrochloride, Mono-lauroyl ethylenediamine saved under nitrogen-gas-atmosphere mind in 500ml 4 opening flask equipped with a thermometer, and a vacuum and nitrogen installation tubing (an amide amine and abbreviation) purity: -- unreacted 97.2% -- lauric-acid:0.8% -- bis--- after teaching amide:2.0%121g (0.5 mols) and carrying out a temperature up to 80 degrees C, it dropped and neutralized, being careful of 48.2g (36%) (0.475 mols) of concentrated hydrochloric acid for whenever [system internal temperature] not to exceed 100 degrees C. another -- cyanamide 31.5g (0.75 mols) -- isopropyl alcohol 31.5g -- dissolving -- amide amine 95% -- it was dropped over 1 hour into the hydrochloride, keeping whenever [system internal temperature] at 80-90 degrees C. Aging was performed at the same temperature after dropping termination for 3 hours, and after adding and carrying out full neutralization of the 2.5g (36%) (0.025 mols) of the concentrated hydrochloric acid, reduced pressure distilling off of the solvent was carried out. yield: -- 170g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.5% from an amide amine, and purity: -- unreacted 88.1% -- amide amine:2.6% and byproduction dicyandiamide:7.0% -- bis--- it was amide:1.4%.

[0033] (2) In the purification agitator of a lauroyl amide ethyl guanidine hydrochloride, and 11 4 opening flask equipped with the thermometer 100g of rough products obtained by (1) was taken, tetrahydrofuran 300g was added, it heated at 65 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 40 degrees C over 25 minutes, after the crystal deposited, it was kept warm at 40 degrees C for 1 hour, and the crystal was deposited enough. After carrying out a crystal a ** exception using a pressure filter, it added calmly, and as it was, it filtered and 40-degree C tetrahydrofuran 200g was washed. The vacuum drying of the 40 degrees C of the crystals was carried out for 2 hours, and the purification lauroyl amide ethyl guanidine hydrochloride was obtained. yield: -- 74g, a liquid chromatograph, and thin layer chromatographic analysis -- purity:

-- unreacted 99.5% -- amide amine:0.4% -- bis--- amide:0.01% and byproduction dicyandiamide: -- it came out 0.1%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the tetrahydrofuran of the bis-amide which carried out the byproduction was 0.5% at 40 degrees C.

[0034] (Example 2) The synthetic agitator of the purification (1) lauroyl amide butyl guanidine-acetic acid salt of a lauroyl amide butyl guanidine-acetic acid salt, Mono-lauroyl butylene diamine saved under nitrogen-gas-atmosphere mind in 500ml 4 opening flask equipped with a thermometer, and a vacuum and nitrogen installation tubing (an amide amine and abbreviation) purity: -- unreacted 98.4% -- lauric-acid:1.0% -- bis--- after teaching amide:0.6%135g (0.5 mols) and carrying out a temperature up to 80 degrees C, it dropped and neutralized, being careful of 30g (0.5 mols) of acetic acids for whenever [system internal temperature] not to exceed 100 degrees C. Independently, cyanamide 25.2g (0.6 mols) was dissolved in isopropyl alcohol 25.2g, and it was dropped over 1 hour into amide amine acetate, keeping whenever [system internal temperature] at 80-90 degrees C. After dropping termination, after performing aging at the same temperature for 3 hours, reduced pressure distilling off of the solvent was carried out. yield: -- 189g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.8% from an amide amine, and purity: -- unreacted 92.4% -- amide amine:1.9% and byproduction dicyandiamide:2.9% -- bis--- they were amide:0.4% and acetylation amide amine:1.6%.

[0035] (2) In the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and 11 4 opening flask equipped with the thermometer 100g of rough products obtained by (1) was taken, methyl-ethyl-ketone 500g was added, it heated at 80 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 55 degrees C over 25 minutes, after the crystal deposited, it was kept warm at 55 degrees C for 1 hour, and the crystal was deposited enough. After carrying out a crystal a ** exception using a filter press, 65-degree C methyl-ethyl-ketone 500g was led and washed [filtered and]. The vacuum drying of the 40 degrees C of the crystals was carried out for 2 hours, and the purification lauroyl amide butyl guanidine-acetic acid salt was obtained. yield: -- 61g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.6% -- amide amine:0.08% -- bis--- less than [amide:0.01%], byproduction dicyandiamide:0.18%, and acetylation amide amine: -- it came out 0.1%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.35% at 65 degrees C.

[0036] (Example 3) The synthetic agitator of the purification (1) lauroyl amide ethyl guanidine-acetic acid salt of a lauroyl amide ethyl guanidine-acetic acid salt, The same mono-lauroyl ethylenediamine 121g (0.5 mols) is taught with having used for 500ml 4 opening flask equipped with a thermometer, and a vacuum and nitrogen installation tubing in the example 1 (1). After carrying out a temperature up to 80 degrees C, it dropped and neutralized, being careful of 30g (0.5 mols) of acetic acids for whenever [system internal temperature] not to exceed 100 degrees C. Independently, cyanamide 25.2g (0.6 mols) was dissolved in isopropyl alcohol 25.2g, and it was dropped over 1 hour into amide amine acetate, keeping whenever [system internal temperature] at 80-90 degrees C. After dropping termination, after performing aging at the same temperature for 3 hours, reduced pressure distilling off of the solvent was carried out. yield: -- 175g, a liquid chromatograph, and thin layer chromatographic analysis -- conversion:93.7% from an amide amine, and purity: -- unreacted 92.5% -- amide amine:1.8% and byproduction dicyandiamide:2.8% -- bis--- they were amide:0.8% and acetylation amide amine:1.6%.

[0037] (2) In the purification agitator of a lauroyl amide ethyl guanidine-acetic acid salt, and 11 4 opening flask equipped with the thermometer 100g of rough products obtained by (1) was taken, methyl-ethyl-ketone 500g was added, it heated at 80 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 50 degrees C over 30 minutes, after the crystal

deposited, it was kept warm at 50 degrees C for 1 hour, and the crystal was deposited enough. After carrying out a crystal a ** exception using a vacuum filter, it added calmly, and as it was, it filtered and 50-degree C methyl-ethyl-ketone 300g was washed. The vacuum drying of the 40 degrees C of the crystals was carried out for 2 hours, and the purification lauroyl amide ethyl guanidine-acetic acid salt was obtained. yield: -- 70g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.5% -- amide amine:0.2% -- bis--- amide:0.01%, byproduction dicyandiamide:0.16%, and acetylation amide amine: -- it came out 0.1%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.2% at 50 degrees C.

[0038] (Example 4) In the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and 11 4 opening flask equipped with the thermometer 100g of lauroyl amide butyl guanidine acetate [which was obtained by the same approach as an example 2 (1)] rough products was taken, methyl-ethyl-ketone 500g was added, it heated at 80 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 55 degrees C over 25 minutes, after the crystal deposited, it was kept warm at 55 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception using the filter press, it put into 11 4 opening flask, and methyl-ethyl-ketone 500g was added, and at 60 degrees C, suspension churning was carried out for 1 hour, and it washed. Furthermore, the crystal was carried out the ** exception using the filter press, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide butyl guanidine-acetic acid salts were obtained. yield: -- 60g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.6% -- amide amine:0.05% -- bis--- amide:0.01%, byproduction dicyandiamide:0.16%, and acetylation amide amine: -- it came out 0.1% or less. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.16% at 60 degrees C.

[0039] (Example 5) In the purification agitator of a lauroyl amide ethyl guanidine hydrochloride, and 11 4 opening flask equipped with the thermometer 100g of lauroyl amide ethyl guanidine hydrochloride [which was obtained by the same approach as an example 1 (1)] rough products was taken, methyl-ethyl-ketone 300g was added, it heated at 80 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 50 degrees C over 30 minutes, after the crystal deposited, it was kept warm at 50 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception using the pressure filter, it put into 11 4 opening flask, and methyl-ethyl-ketone 300g was added, and at 50 degrees C, suspension churning was carried out for 1 hour, and it washed. Furthermore, the crystal was carried out the ** exception using the pressure filter, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide ethyl guanidine hydrochlorides were obtained. yield: -- 74g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.6% -- amide amine:0.2% -- bis--- amide:0.01% and byproduction dicyandiamide: -- it came out 0.12%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the methyl ethyl ketone of the bis-amide which carried out the byproduction was 0.2% at 50 degrees C.

[0040] (Example 6) In the purification agitator of a lauroyl amide butyl guanidine-acetic acid salt, and 11 4 opening flask equipped with the thermometer 100g of lauroyl amide butyl guanidine acetate [which was obtained by the same approach as an example 2 (1)] rough products was taken, tetrahydrofuran 500g was added, it heated at 65 degrees C, and the rough product was dissolved completely. At 1-degree-C a rate for /, it cooled to 25 degrees C over 40 minutes, after the crystal deposited, it was kept warm at 25 degrees C for 1 hour, and the crystal was deposited enough. The crystal was carried out the ** exception using the centrifugal filtration machine, it put into 11 4

opening flask, and tetrahydrofuran 300g was added, and at 25 degrees C, suspension churning was carried out for 1.5 hours, and it washed. Furthermore, the crystal was carried out the ** exception using the centrifugal filtration machine, the vacuum drying was carried out for 2 hours, and 40 degrees C of purification lauroyl amide butyl guanidine-acetic acid salts were obtained. yield: -- 80g, a liquid chromatograph, and thin layer chromatographic analysis -- purity: -- unreacted 99.3% -- amide amine:0.3% -- bis--- amide:0.02%, byproduction dicyandiamide:0.15%, and acetylation amide amine: -- it came out 0.2%. When 50g of this refined material was taken and it dissolved in ethanol 30g and 20g of water, it was 25-degree-C six-month Hazama transparence solution. In addition, the solubility to the tetrahydrofuran of the bis-amide which carried out the byproduction was 0.1% at 25 degrees C.

[0041] (Example 7) The following shampoo constituents were prepared using the amide group content guanidine salt obtained in the examples 1-6.

this invention article 0.7 Lauric-acid sugar ester 10 N and N-dimethyl-N-lauryl amine oxide 10 At the time of palm oil fatty acid, ethanol amide 4 Sodium benzoate 0.9 Sodium sulfate 2 Water Remainder (pH7: adjust by the sodium hydroxide)

Also when which product was used, 25-degree-C six-month Hazama and a solution were stable.

[0042] (Example 8) The following cleaning agent constituents for kitchens were prepared using the amide group content guanidine salt obtained in the examples 1-6.

this invention article 5 Polyoxyethylene (p= 3) sodium lauryl sulfate 25 Glycerol 3 Ethanol 7 Palm-oil-fatty-acid diethanolamide 5 Sodium benzoate 3 Perfume 0.4 Water the remainder -- also when which product was used, 25-degree-C six-month Hazama and a solution were stable.